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PATENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 November 1997 (11.11.97)	
International application No. PCT/GB97/00929	**Applicant's or agent's file reference** P17526/CPA/RMC
International filing date (day/month/year) 02 April 1997 (02.04.97)	**Priority date** (day/month/year) 02 April 1996 (02.04.96)
Applicant FARRAR, Gwenyth, Jane et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   27 October 1997 (27.10.97)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Aino Metcalfe
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992) 1756921

Replaced by Article 34 Amend

09/155708

RECD 07 JUL 1998
WIPO PCT

19

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
P17526/RMC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB97/00929	02/04/1997	02/04/1996
International Patent Classification (IPC) or national classification and IPC		
C12N15/11		
Applicant		
PROVOST, FELLOWS AND SCHOLARS OF THE ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/10/1997	03.07.98
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	SCHEFFZYK, I Telephone No. (+49-89) 2399-8602

Form PCT/IPEA/409 (Cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB97/00929

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-52	as originally filed	

Claims, No.:

1-11	with telefax of	25/05/1998

Drawings, sheets:

1/30-30/30	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1, 4-11
	No:	Claims 2, 3
Inventive step (IS)	Yes:	Claims 1, 4-11
	No:	Claims 2, 3
Industrial applicability (IA)	Yes:	Claims 2, 3, 5, 6-9
	No:	Claims 1, 4, 10, 11: see item VIII/5).

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION V ----------

Claim 2 cannot be considered to be novel since according to the present wording of said claim any hitherto known suppression agent, such as for instance antisense RNAs/DNAs or ribozymes, are covered by the scope of said claim. Moreover, the plasmid taught in Human Molecular Genetics, 1995, vol. 4, no. 9, pp. 1597-1602, Hart S.L. et al. (1) comprising a sequence encoding CFTR wherein the sequence contains a silent point mutation at a wobble site also anticipates novelty of said claim (see e.g. the section "mutagenesis").

According to the present wording of claim 3 it is unclear whether the sequence of the replacement gene product differs from the endogenous gene to be replaced in only one or in more wobble sites. Thus, at present the subject-matter of the said claim is not clearly delimitated from the disclosure of (1) either.

Thus, claims 2 and 3 do not comply with the requirements of Art. 33(2)(3) PCT.

In this context it is noted that an indication of use in a product claim is not considered limiting, i.e. the scope of such a claim corresponds to the product as such (see Guidelines C-III, 4.8 PCT).

Claims 1, 4-11 can be considered to be novel and inventive since none of the available documents teaches or suggests presently claimed strategy for suppressing a (mutated) gene which combines suppression of an endogenous gene containing a mutation with a deleterious effect by suppression agent(s) and the replacement thereof with a nucleic acid sequence which only differs from the gene to be suppressed in one or more wobble sites so that the replacement nucleic acid sequence still codes for the wild type protein but is at least partially protected from suppression by suppression agent(s).

SECTION VI----------

WO 97/11169	27.03.97	23.09.96	21.09.95

SECTION VII----------

Present application as filed only teaches replacement genes exhibiting modifications at third base wobble positions which provide the wild type gene product. Thus, no basis can be found in the application as filed for modifications which provide equivalent amino acids as required in claims 1 and 4 (Art. 34 (2)b) PCT).

SECTION VIII----------

1). The reference in claim 7 to claims 5 and 6, respectively appears to be incorrect since the said claims are concerned with autosomal dominant diseases.

2). Claim 8 which refers to claim 6 appears to be in contradiction to claim 6 since according to claim 6 the suppression effector as well as the replacement nucleic acids are administered in vectors.

3). Claim 11 is not in line with the teaching of present application since according to present application the replacement gene is only modified at third base wobble positions so that it still encodes the wild type protein.

4). Present claims are not fully supported by the specification since the application is limited to in vitro examples whereas the said claims also encompass in vivo application of the claimed strategy. However, acording to Art. 6 PCT the whole scope claimed must be supported by the specification.

5). For the assessment of the present claims 1, 4, 10 and 11 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

1. A strategy for suppressing or partially suppressing an endogenous gene and replacing the suppressed gene sequence with a nucleic acid sequence which differs from the endogenous gene and wherein the suppressing agent(s) comprises at least one suppressor from the group comprising antisense nucleic acid, peptide nucleic acids, DNA capable of forming triple helix or ribozymes targeted to the endogenous gene or gene transcripts and wherein the replacement nucleic acid sequence encodes at least part of a gene product and is not suppressed by suppression agent(s) or is suppressed less efficiently by suppression agent(s) and wherein the replacement nucleic acid sequence comprises amino acid codons which encode at least part of the gene product, and have modifications at wobble site(s) such that replacement nucleic acids still code for the wild type or equivalent amino acids.

2. A medicament comprising either one or both of a gene suppressing agent and a nucleic acid encoding at least part of a replacement gene product for use in a strategy as claimed in Claim 1.

3. A medicament comprising a nucleic acid sequence encoding at least part of a gene product wherein the sequence differs from the endogenous gene in wobble sites.

4. A strategy for suppressing or partially suppressing an endogenous gene and introducing a replacement gene said strategy comprising the steps of:

a. providing suppression nucleic acids or other suppression effector(s) able to recognise, bind or cleave an endogenous gene, gene transcript(s) or gene product to be suppressed and

b. providing genomic DNA or cDNA (complete or partial) encoding a replacement gene wherein the suppression nucleic acids are unable to recognise, bind or cleave or able to recognise, bind or cleave less efficiently equivalent regions in the genomic DNA or cDNA to prevent suppression of the replacement gene wherein the coding sequence of replacement nucleic acids has been altered to prevent or reduce efficiency of suppression and wherein replacement nucleic acids have modifications in one or more wobble sites such that replacement nucleic acids still code for the wild type or equivalent amino acids.

5. The use of a strategy as claimed in any of the preceding Claims in the preparation of a medicament for the treatment of an autosomal dominant disease caused by an endogenous target gene wherein the disease is caused by different mutations in the same gene in different patients.

6. The use of:

a. a vector or vectors containing suppression effector(s), said suppression effector(s) being able to recognise, bind or cleave coding sequences of a target endogenous gene and

b. vector(s) containing replacement nucl ic acids in the form of genomic DNA, cDNA or

RNA, which contain alter d wobble sites such that replacement nucleic acids cannot be recognised, bound or cleaved by suppressor(s) or are recognised, bound or cleaved less efficiently by suppressor(s) which are targeted towards coding sequence of the endogenous gene and which provide the wild type gene product and wherein the difference between said endogenous gene and the replacement gene still enables the expression of the replacement gene,

in the preparation of a medicament for the treatment of an autosomal dominant disease caused by the endogenous gene wherein the disease is caused by different mutations in the same gene in different patients.

7. A use as claimed in Claims 5 or 6 wherein the disease is a polygenic disorder.

8. A use as claimed in Claim 6 or 7 wherein suppressor(s) or replacement gene(s) are administered alone or in vector(s) chosen from DNA plasmid vectors, RNA or DNA viral vectors.

9. A use as claimed in Claim 8 wherein the suppressor(s) or replacement gene(s) are combined with lipids, polymers or other derivatives.

10. A kit for use in the treatment of an autosomal dominant or polygenic disease caused by mutation(s) in a target endogenous gene, the kit comprising at least one suppression effector able to recognise, bind or cleave coding sequence(s) of the endogenous gene to b suppr ssed and at least

AMENDED SHEET

one replacement gene to replace the endogenous gene having modifications to wobble sites such that the replacement gene cannot be recognised, bound or cleaved or can be recognised, bound or cleaved less efficiently by suppressor(s) targeted to coding sequence(s) of the endogenous gene, said replacement nucleic acid sequence providing the wild type gene product, and wherein the difference between said wild type target gene and the replacement gene still enables expression of the replacement gene.

11. A use as claimed as in Claims 1 to 10 wherein the replacement gene is altered from the wild type gene and provides a beneficial effect when compared to the wild type gene.

MUR-7520

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
P17526/RMC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB97/00929	02/04/1997	02/04/1996
International Patent Classification (IPC) or national classification and IPC		
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Date of submission of the demand	Date of completion of this report
27/10/1997	03.07.98
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	SCHEFFZYK, I Telephone No. (+49-89) 2399-8602

Form PCT/IPEA/409 (Cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB97/00929

I. Basis of the report

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1-52 as originally filed

Claims, No.:

1-11 with telefax of 25/05/1998

Drawings, sheets:

1/30-30/30 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
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4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Int mational application No. PCT/GB97/00929

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1, 4-11
	No:	Claims 2, 3
Inventive step (IS)	Yes:	Claims 1, 4-11
	No:	Claims 2, 3
Industrial applicability (IA)	Yes:	Claims 2, 3, 5, 6-9
	No:	Claims 1, 4, 10, 11: see item VIII/5).

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

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see separate sheet

VIII. Certain observations on the international application

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see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB97/00929

SECTION V

Claim 2 cannot be considered to be novel since according to the present wording of said claim any hitherto known suppression agent, such as for instance antisense RNAs/DNAs or ribozymes, are covered by the scope of said claim. Moreover, the plasmid taught in Human Molecular Genetics, 1995, vol. 4, no. 9, pp. 1597-1602, Hart S.L. et al. (1) comprising a sequence encoding CFTR wherein the sequence contains a silent point mutation at a wobble site also anticipates novelty of said claim (see e.g. the section "mutagenesis").

According to the present wording of claim 3 it is unclear whether the sequence of the replacement gene product differs from the endogenous gene to be replaced in only one or in more wobble sites. Thus, at present the subject-matter of the said claim is not clearly delimitated from the disclosure of (1) either.

Thus, claims 2 and 3 do not comply with the requirements of Art. 33(2)(3) PCT.

In this context it is noted that an indication of use in a product claim is not considered limiting, i.e. the scope of such a claim corresponds to the product as such (see Guidelines C-III, 4.8 PCT).

Claims 1, 4-11 can be considered to be novel and inventive since none of the available documents teaches or suggests presently claimed strategy for suppressing a (mutated) gene which combines suppression of an endogenous gene containing a mutation with a deleterious effect by suppression agent(s) and the replacement thereof with a nucleic acid sequence which only differs from the gene to be suppressed in one or more wobble sites so that the replacement nucleic acid sequence still codes for the wild type protein but is at least partially protected from suppression by suppression agent(s).

SECTION VI

WO 97/11169	27.03.97	23.09.96	21.09.95

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

Int mational application No. PCT/GB97/00929

SECTION VII

Present application as filed only teaches replacement genes exhibiting modifications at third base wobble positions which provide the wild type gene product. Thus, no basis can be found in the application as filed for modifications which provide equivalent amino acids as required in claims 1 and 4 (Art. 34 (2)b) PCT).

SECTION VIII

1). The reference in claim 7 to claims 5 and 6, respectively appears to be incorrect since the said claims are concerned with autosomal dominant diseases.

2). Claim 8 which refers to claim 6 appears to be in contradiction to claim 6 since according to claim 6 the suppression effector as well as the replacement nucleic acids are administered in vectors.

3). Claim 11 is not in line with the teaching of present application since according to present application the replacement gene is only modified at third base wobble positions so that it still encodes the wild type protein.

4). Present claims are not fully supported by the specification since the application is limited to in vitro examples whereas the said claims also encompass in vivo application of the claimed strategy. However, acording to Art. 6 PCT the whole scope claimed must be supported by the specification.

5). For the assessment of the present claims 1, 4, 10 and 11 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

1. A strategy for suppressing at least a part of the coding region of an endogenous gene and replacing the suppressed gene sequence with a nucleic acid sequence which differs from the endogenous gene.

2. A strategy as claimed in Claim 1 wherein the suppressing agent comprises at least one suppressor from the group comprising antisense nucleic acid, DNA capable of forming triple helix or ribozymes to the endogenous gene.

3. A strategy as claimed in Claim 1 or 2 wherein the replacement nucleic acid sequence encodes at least part of a gene product and does not interact with the suppressing agent.

4. A strategy as claimed in any of the preceding claims wherein the replacement nucleic acid sequence comprises amino acid codons which encode at least part of the gene product, and differ from the gene to be suppressed in at least the third base of at least one of the codons.

5. A medicament comprising either one or both of a gene suppressing agent and a nucleic acid encoding at least part of a replacement gene product for use in a strategy as claimed in any of the preceding claims.

6. A medicament comprising a nucleic acid sequence encoding at least part of a gene product wherein the sequence differs from an endogenous gene in at least the third base of at least one amino acid codon.

7. A strategy for suppressing specifically or partially specifically an endogenous gene and introducing a replacement gene, said strategy comprising the steps of:

1. providing suppressing nucleic acids or other suppression effectors able to bind to an endogenous gene, gene transcript or gene product to be suppressed and

2. providing genomic DNA or cDNA (complete or partial) encoding a replacement gene wherein the suppressing nucleic acids are unable to bind to equivalent regions in the genomic DNA or cDNA to prevent expression of the replacement gene.

8. A strategy as claimed in Claim 8 wherein the coding sequence of replacement nucleic acids has been altered to prevent or reduce efficiency of suppression.

9. A strategy as claimed in Claim 8 or 9 wherein replacement nucleic acids have modifications in one or more third base (wobble) positions such that replacement nucleic acids still code for the wild type or equivalent amino acids.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02357

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C12N9/00 C12N15/85 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEUKEMIA, vol. 8, April 1994, pages s152-s155, XP000652853 ROBINSON-BENION, C. ET AL.: "Gene transplantation: Combined antisense inhibition and gene replacement strategies" see p.152, right-hand column, l. 17-19; p.153, left-hand column, l. 1-4 and 18-21; Abstract	1-4,7,8, 11-15
A	see last sentence of the Abstract and Discussion	10,16-20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 April 1997	07. 05. 97
Name and mailing address of the ISA	Authorized officer
	Alt, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02357

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 11494 A (THOMAS JEFFERSON UNIVERSITY) 26 May 1994 see page 5;page 11, second paragraph continued on page 12; pages 19-20;	1-4,7-11
A		12-20

X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 86, - 1989 pages 10006-10010, XP000652039 CHANG, J.L.C. ET AL.: "Antisense RNA complementary to 3'coding and noncoding sequences of creatine kinase is a potent inhibitor of translation in vivo" see page 10006, right-hand column, second and third paragraph	1-4,7-9, 11

X	WO 93 21202 A (YISSUM RESEARCH DEVELOPMENT COMPANY) 28 October 1993 see page 36, first paragraph	1-4,7,8, 11

X	WO 94 22487 A (THOMAS JEFFERSON UNIVERSITY) 13 October 1994 see Example 2	1-4,7,8
A		10,12-20

A	WO 94 03596 A (UNIVERSITY OF HAWAII) 17 February 1994 see pages 30-36	5

A	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 88, 1991, pages 8227-8231, XP002028900 POSTEL, E.H. ET AL.: "Evidence that a triplex-forming oligodeoxyribonucleotide binds to the c-myc promoter in HeLa cells, thereby reducing c-myc RNA levels" see the whole document	6

A	PEDIATRIC RESEARCH, vol. 37, no. 4, April 1995, page 150 XP000652811 MARINI, J.C. AND WANG, C.: "Antisense oligonucleotides selectively suppress production of mutant alpha2(I) collagen in osteogenesis imperfecta type IV fibroblasts: an approach to gene therapy for a dominant disorder of matrix structural protein " see the whole Abstract	1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02357

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411494 A	26-05-94	EP 0674705 A	04-10-95
		JP 8503366 T	16-04-96
WO 9321202 A	28-10-93	AT 150029 T	15-03-97
		AU 4039993 A	18-11-93
		CA 2118235 A	28-10-93
		EP 0636137 A	01-02-95
		JP 8504083 T	07-05-96
WO 9422487 A	13-10-94	NONE	
WO 9403596 A	17-02-94	AU 4794593 A	03-03-94

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P15892/CPA/RMC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/GB96/02357	International filing date *(day/month/year)* 23/09/1996	Priority date *(day/month/year)* 21/09/1995
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant PROVOST, FELLOWS AND SCHOLARS OF THE ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

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   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
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   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/04/1997	21. 01. 98
Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Alt, G Telephone No. (+49-89) 2399-8545

Form PCT/IPEA/409 (Cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB96/02357

I. Basis of the report

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Description, pages:

1-49 as originally filed

Claims, No.:

1-35 as received on 06/12/1997 with letter of 01/12/1997

Drawings, sheets:

1/40-40/40 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
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☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 28, 29.

because:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB96/02357

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27, 30-35
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2-13, 15-27, 34
	No:	Claims	1,14, 30-33
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	30-32

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB96/02357

Section III
No opinion

1. While the Applicant's submission with regard to Claims 28 and 29 (former Claims 14 and 15) has been considered, the previously expressed opinion is nevertheless maintained, i.e. the International Preliminary Examination Report does not cover Claims 28 and 29 because it is neither apparent from the application documents nor from any of the cited prior art documents which compounds have the function of "naturally occurring endogenous suppressors". Therefore these claims are regarded as unclear.

Section V
Novelty

1. D1=WO-A-9321202 relates to the use of antisense oligonucleotides in order to modulate bone marrow cell development. The oligonucleotides are either directed to the 5' non-coding region of the human CHED gene (page 36, first paragraph) or to a region spanning the AUG codon of the human ACHE gene or the human BCHE gene. In the case of the CHED gene suppression effects are not reported. There is no mention in D1 of the use of suppression effectors in a suppression/ replacement strategy in connection with a gene causing an autosomal dominant disease.

   D2=PNAS, vol. 86, pages 10006-10010, 1989, Lai et al. discloses that antisense RNA complementary to the last third of the coding and all of the non-coding region of mRNA inhibits translation of endogenous creatine kinase.
   D2 does neither mention suppression/replacement strategy in connection with autosomal disease nor are are suppression effectors directed to non-coding, untranslated or control regions only.

   D3=Pediatric Research, vol. 37, no. 4, April 1995, abstract no. 885 discloses antisense oligonucleotides directed against the mutant exon 15/17 mRNA junction or against the related genomic point mutation of the alpha2(I) chain of collagen.

   D4=WO-A-9422487 discloses transgenic mice which are transfected with a

human COL1A1 mini-gene construct and the antisense version of the 3' part of the same gene.

Both D3 and D4 disclose suppression effectors directed to coding regions.

D5=Leukemia, vol. 8, 1994, pages s152-s155, Robinson-Benion et al. discloses that stable cell lines were produced containing either a vector expressing a c-fos gene deleted at the 3' terminus or a vector expressing a c-fos gene lacking 84 base pairs of the 5' untranslated region and a vector expressing antisense RNA complementary to a portion of the 5' untranslated c-fos gene. Upon induction of the antisense-vector endogenous c-fos gene expression was reduced whereas expression of the mutant gene was not affected. Moreover it is mentioned on page S154 that the approach may be useful in certain gene therapy applications where it is necessary to eliminate the endogenous gene and introduce a mutant gene.
HOwever, D5 does not disclose the suppression/replacement strategy in connection with an autosomal dominant disease.

Thus, the subject-matter of Claims 1-27 and 30-35 is regarded as novel.

Inventive step

2. D6=WO-A-9411494 is regarded as the closest prior art document. It deals with the inhibition of expression of mutated and wild type collagen genes. Mutations in collagen genes, like for example in the human type 1 collagen Col1A2 gene can cause autosomal dominantly inherited osteogenesis imperfecta (see page 44 of the present application). D6 discloses on page 33 that examination of collagen mutations has shown that different mutations in the same gene give rise to the same disease phenotype and that before a gene therapy can be envisaged a test would have to be made for each patient in order to determine the type of mutation. In order to solve this problem D6 suggests that antisense oligonucleotides are directed to neutral sequence variations which occur in many collagen genes. The effect is that a small panel of oligonucleotides will be adequate to specifically inhibit expression of a larg number of differ nt mutations that may occur in the sam allele.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

Int mational application No. PCT/GB96/02357

3. The present application deals with gene therapy of autosomal dominant diseases. In order to overcome the problems of differentiation between the normal and the disease alleles and to selectively switch off the disease allele the application essentially suggests to use suppression effectors directed to untranslated, non-coding or control regions of the mutated gene in combination with vectors encoding a functional replacement gene the expression of which is not affected by the suppression effectors. Basically, this strategy has the advantage that the design of the suppression effectors is independent from individual mutations and can be used for most of the disease mutations identified in a given gene.

Thus, the problem to be solved by the present application can be formulated as providing an improved method for the treatment of autosomal dominant diseases.

The solution to this problem provided by the application is a combined strategy consisting of suppression of the disease gene and its replacement by an intact gene whereby the suppression effectors are targeted to untranslated, non-coding and/or control regions.

4. D5 discloses a test system for a suppression/replacement strategy. The system is exemplified in cell culture with the human c-fos gene. The antisense oligonucleotides are directed to the 5' untranslated region. It is mentioned in the last paragraph of D5 that "this approach may be useful in certain gene therapy applications where it is necessary to eliminate the endogenous gene and introduce a mutant gene. The last sentence of the abstract states that "this gene transplant method for inhibition of endogenous genes and replacement with preferred genes has implications for gene therapy of hereditary haematologic disorders and for the correction or repair of oncogenes or tumour suppressor gens in leukemias and lymphomas". It appears that these statements render the application of the method of D5 obvious for the treatment of those autosomal dominant diseases where the disease is not caused by different mutations in the same gene in different patients.

Therefore, the subject-matt r of Claims 1, 14, 30-33 and 35 is not regarded as involving an inventive step (Article 33(3) PCT).

5. In contrast, D5 is silent about any advantages the application of the suppression/ replacement method would have in connection with polygenic autosomal dominant disorders or with autosomal dominant disorders which are caused by different mutations in the same gene in different patients.

   Thus, the subject-matter of Claims 2-13, 15-27 and 34 is regarded to involve an inventive step.

Industrial applicability

6. For the assessment of the present Claims 30-32 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

Certain observations

1. The following objections to the present claims arise under Article 6 PCT:
   i) The independent Claims 1, 14, 23, 30, 33 and 35 do not contain the same or corresponding essential technical features.
   ii) Claims which contain all features of an independent claim are not formulated as dependent claims.
   iii) Some expressions in the claims are vague or inconsistent with relation to other claims.

   The deficiencies are listed in detail below and suggestions for amendment are made:
   Claim 1: the term "directed towards" in line 6 should be replaced by "able to bind to" (see Claim 14); in lines 6 and 7 the term ""untranslated and/or control s quences" should b r placed by "non-coding, untranslated and/or control sequences; in line 10 the term "non-coding" should be replaced by the term "non-coding and/or untranslated and/or control sequences"(for example Claim 14); in

lines 12 and 13 the term "suppressor(s)" should be replaced by the term "suppression effector(s)"; the expression "such that replacement nucleic acids cannot be recognized by suppressor(s) or are recognised less efficiently by suppressor(s)" should be replaced by "such that the suppression effector(s) which are targeted towards the non-coding, untranslated and/or control sequences of the endogenous gene are unable to recognise, bind or cleave or are able to recognise, bind or cleave less efficiently the non-coding and/or untranslated and/or control sequences of the replacement nucleic acids" (see Claim 19).

In Claim 8 the term "naked DNA" should be deleted (In the context of the claim the term is unclear. A desired nucleic acid fragment can be administered as naked DNA or it can be inserted into a vector and the vector is administered as naked DNA. This way of administration is in contrast to combination of a DNA fragment or vector with for example lipids.) and instead inserted into Claim 9:"...wherein the vector is administered as naked DNA or is combined with lipids, polymers or other derivatives"

Claim 11 should read:"...wherein the suppression effectors are ribozymes"

Claim 12 should read:"...wherein the suppression effectors are triple helix forming oligonucleotides"

Claim 13 should read:"...wherein the non-coding sequences of the replacement gene are altered such that the replacement gene provides a wild type gene with beneficial characteristics" (see page 10, first full paragraph).

Claim 14: lines 18 to 26 should be modified as suggested for Claim 1.

Claim 18, line 10 should read "and/or peptides" (see Claim 5)

Claim 19, line 13 should read "suppression effector(s)"; lines 15-16 should read "non-coding, untranslated and/or control sequences".

Claims 24 and 25 should be modified according to Claims 8 and 9.

Claim 27 should be modified as suggested for Claim 13.

The wording of Claim 30 should be adapted to that of Claim 1.

Claim 35 should be dependent on Claim 1.

CLAIMS

1. The use of :

A) A vector or vectors containing suppression effectors, said suppression effectors being directed towards, untranslated and/or control sequences of a target endogeneous gene; and

b) vector(s) containing genomic DNA, cDNA or RNA encoding a replacement gene sequence, which contains altered non-coding sequences such that replacement nucleic acids cannot be recognised by suppressor(s) or are recognised less efficiently by suppressor(s) which are targeted toward the non-coding and/or untranslated and/or control sequences of the endogenous gene and which provide the wild type gene product, and wherein the difference between said endogenous gene and the replacement gene still enables expression of the replacement gene;

in the preparation of a combined medicament for the treatment of an autosomal dominant disease caused by the endogenous target gene.

2. A use as claimed in Claim 1, wherein the disease is caused by different mutations in the same gene in different patients.

3. A use as claimed in Claim 1, wherein the disease is a polygenic disorder.

4. A use as claimed in any of Claims 1 to 3, wherein control sequences of the replacement gene sequence belong to a different mammalian species, a different human gene or are similar but altered from those in the gene to be suppressed and thus permit transcription and translation of the

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replacement nucleic acids.

5. A use as claimed in any of Claims 1 to 4, wherein the suppression effectors are nucleic acids, antisense nucleic acids, peptide nucleic acids and/or peptides.

6. A use as claimed in Claim 5, wherein the suppression effectors are directed to 5′ and/or 3′ untranslated regions and/or to introns and/or to control regions or to any combination of such untranslated regions.

7. A use as claimed in any of Claim 1 to 6, wherein the suppression effectors are antisense nucleic acids.

8. A use as claimed in any of Claims 1 to 7, wherein the vector is chosen from naked DNA, DNA plasmid vectors, RNA or DNA virus vectors.

9. A use as claimed in Claim 8, wherein the vector is combined with lipids, polymers or other derivatives.

10. A use as claimed in any of Claims 1 to 9, wherein suppression effectors are targeted to promoter regions of the gene to be suppressed.

11. A use as claimed in any of Claims 1 to 10, wherein ribozymes are used.

12. A use as claimed in any of Claims 1 to 11, wherein triple helixes nucleotides are used.

13. A use as claimed in any of Claims 1 to 12, wherein

the replacement gene is altered from the wild type gene and provides a beneficial effect when compared to the wild type gene.

14. A strategy for suppressing at least one target endogenous gene causing an autosomal dominant disease and introducing a replacement gene sequence, said strategy comprising the steps of:

1. providing a suppression effector able to bind to at least one non-coding, untranslated and/or control sequence of the target gene to be suppressed; and

2. providing genomic DNA,cDNA or RNA encoding a replacement gene sequence,

which contains altered non-coding sequences such that replacement nucleic acids cannot be recognised by suppressor(s) or are recognised less efficiently which are targeted toward the non coding and/or untranslated and/or control sequence(s) of the endogenous gene and which provides the wild type of gene product, and wherein the difference between said wild type gene and the replacement gene still enables expression of the replacement gene.

15. A strategy as claimed in Claim 14, wherein the disease is caused by different mutations in the same gene in different patients.

16. A strategy as claimed in Claim 14, wherein the disease is a polygenic disorder.

17. A strategy as claimed in any of Claims 14 to 16, wherein non-coding, untranslated and/or control

AMENDED SHEET

sequences of the replacement gene sequence belong to a different mammalian species, a different human gene or are similar but altered from those in the gene to be suppressed and thus permit transcription and translation of the replacement nucleic acids.

18. A strategy as claimed in any of Claims 14 to 17, wherein the suppression effectors are nucleic acids, anti-sense nucleic acids peptide nucleic acids or peptides.

19. A strategy as claimed in Claim 18, wherein the suppressor effector(s) are unable to recognise, bind or cleave or are able to recognise, bind or cleave less efficiently, untranslated and/or control sequences in the genomic DNA, cDNA or RNA to prevent the expression of the replacement gene sequence.

20. A strategy as claimed in any one of Claims 18 and 19, wherein the suppression effectors are directed to 5' and/or 3' untranslated regions and/or to introns and/or to control regions or to any combination of such untranslated regions.

21. A strategy as claimed in any of Claims 14 to 20, wherein the strategy further employs ribozymes.

22. A strategy as claimed in any of Claims 14 to 21, wherein the strategy further employs nucleotides which form triple helixes.

23. A strategy as claimed in any of claims 14 to 22, wherein the suppression effectors are incorporated into a vector.

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24. A strategy as claimed in Claim 23, wherein the vector is chosen from naked DNA, DNA plasmid vectors, RNA or DNA virus vectors.

25. A strategy as claimed in Claims 23 or 24, wherein the vector is combined with lipids, polymers or other derivatives.

26. A strategy as claimed in any of Claims 14 to 25, wherein suppression effectors are targeted to promote regions of the gene to be suppressed.

27. A strategy as claimed in any of Claims 14 to 26, wherein the replacement gene is altered from the wild type gene and provides a beneficial effect when compared to the wild type gene.

28. Replacement nucleic acids for use in a use as claimed in any of Claims 1 to 13 or in a strategy as claimed in any of claims 14 to 27, with altered non-coding sequences such that replacement nucleic acids cannot be recognised by naturally occurring endogenous suppressors.

29. Replacement nucleic acids as claimed in claim 28, which comprises altered non-coding sequences to provide gene product being at least partially protected from suppression by naturally occurring endogenous suppression effectors.

30. A method of treatment for an autosomal dominant disease caused by at least one endogenous gene, said method comprising sequential or concomitant introduction of (a) antisense nucleic acids to the non-coding regions of the endogeneous gene to be suppressed; to the 5′ and/or 3′ untranslated

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regions of a gene or intronic regions or to control regions of the gene to be suppressed,
(b) replacement gene sequence with control sequences which allow it to be expressed which contains altered non-coding sequences such that replacement nucleic acids cannot be recognised by suppressors which are targeted toward the non-coding sequence and/or untranslated and/or control sequences of the endogenous gene and which provides the wild type gene product, and wherein the difference between said target gene and the replacement gene still enables efficient expression and functioning of the replacement gene.

31. A method of treatment as claimed in Claim 30, wherein the nucleic acids for gene suppression is administered before or after or at the same time as the replacement gene is administered.

32. A method of treatment as claimed in Claim 30 or 31, wherein nucleotides can be administered as naked DNA or RNA, as viral or non viral vectors, with or without carriers such as lipids, polymers or other derivatives.

33. A kit for use in the treatment of an autosomal dominant disease caused by an mutation in a target endogeneous gene, the kit comprising at least one suppression effector able to bind to the 5' and / or 3' untranslated regions or intronic regions or control regions of the endogenous gene to be suppressed and at least one replacement nucleic acid to replace the endogenous gene having a control sequence to allow it to be expressed and which contains altered non-coding and/or untranslated and/or contol sequences such that the

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replacement nucleic acid cannot be recognised by the suppressors which are targeted toward a non-coding and/or a translated and/or control sequences of the endogenous gene, said replacement nucleic acid sequence providing the wild type gene product, and wherein the difference between said wild type target gene and the replacement gene still enables expression of the replacement gene.

34. A kit as claimed in claim 33, wherein the disease is a polygenic disorder.

35. The use of a vector or vectors containing suppression effectors in the form of nucleic acids, said nucleic acids being directed towards untranslated regions or control sequences of the target gene and vector(s) containing genomic DNA or cDNA encoding a replacement gene sequence to which nucleic acids for suppression are unable to bind, in the preparation of a combined medicament for the treatment of an autosomal dominant disease.

09/155708

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P17526/CPA/RMC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 97/00929	02/04/1997	02/04/1996
Applicant		
PROVOST, FELLOWS AND SCHOLARS OF THE ... et al		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [X] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/00929

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-4, 7-9 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/00929

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C12N9/00 A61K48/00 A61K31/70 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEUKEMIA, vol. 8, no. SUPPL. 01, April 1994, pages 152-155, XP000652853 ROBINSON-BENION C ET AL: "GENE TRANSPLANTATION: COMBINED ANTISENSE INHIBITION AND GENE REPLACEMENT STRATEGIES"	1-3,7,8
Y	see the whole document ---	4,9
Y	HUMAN MOLECULAR GENETICS, (1995 SEP) 4 (9) 1597-602., XP002038178 HART S L ET AL: "The introduction of two silent mutations into a CFTR cDNA construct allows improved detection of exogenous mRNA in gene transfer experiments." see the whole document ---	4,9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 1997	29.08.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Andres, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 475 623 A (UNIV CALIFORNIA) 18 March 1992 see page 7, line 37 - line 45	5,6
A	see page 8, line 6 - line 25	4,7-9

X	US 5 240 846 A (COLLINS FRANCIS S ET AL) 31 August 1993 see column 3, line 3 - line 8 see column 6, line 58 - column 7, line 8 see example I	5,6

A	WO 93 12257 A (HYBRITECH INC) 24 June 1993 see page 8, line 12 - line 33 see page 32, line 30 - page 33, line 24 see page 36; example III	4,9

A	WO 94 11494 A (UNIV JEFFERSON ;PROCKOP DARWIN (US); COLIGE ALAIN (BE); BASERGA RE) 26 May 1994	

P,X	WO 97 11169 A (TRINITY COLLEGE DUBLIN ;FARRAR GWENYTH JANE (IE); HUMPHRIES PETER) 27 March 1997 see page 6, line 25 - page 11, line 5 see examples	1-3,7,8

MUR-7080

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P15892/CPA/RMC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 96/ 02357	23/09/1996	21/09/1995
Applicant		
PROVOST, FELLOWS AND SCHOLARS OF THE ... et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [X] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established by this Authority to read as follows:

   STRATEGY FOR SUPPRSSING THE EXPRESSION OF AN ENDOGENEOUS GENE BY USING COMPOUNS THAT ARE ABLE TO BIND TO THE NON-CODING REGIONS OF THE GENE TO BE SUPPRESSED

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02357

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C12N9/00 C12N15/85 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEUKEMIA, vol. 8, April 1994, pages s152-s155, XP000652853 ROBINSON-BENION, C. ET AL.: "Gene transplantation: Combined antisense inhibition and gene replacement strategies" see p.152, right-hand column, l. 17-19; p.153, left-hand column, l. 1-4 and 18-21; Abstract	1-4,7,8, 11-15
A	see last sentence of the Abstract and Discussion	10,16-20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 April 1997	07. 05. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Alt, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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